

Rec'd PCT/PTC 11 APR 2005  
PCT/CA 03/01524

13 NOVEMBER 2003 13.11.03

CA 03/1524

PA 1084774

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

October 27, 2003

REC'D 04 DEC 2003

WIPO PCT

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM  
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK  
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT  
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A  
FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/416,911

FILING DATE: October 09, 2002

PRIORITY DOCUMENT  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH  
RULE 17.1(a) OR (b)



By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS

*L. Edelen*

L. EDELEN  
Certifying Officer

BEST AVAILABLE COPY

60416911.10090E

Please type a plus sign (+) inside this box



Approved for use through 10/31/2002 OMB 0851-0032  
 U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)			
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)	
Wayne, R.	Danter	147 Chesham Ave., London, Ontario N6G 3V2, Canada	
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto			
TITLE OF THE INVENTION (280 characters max)			
PROTEIN TYROSINE KINASE INHIBITORS			
Direct all correspondence to:			
<input checked="" type="checkbox"/> Customer Number	24223		 Place Customer Number Bar Code Label here PATENT & TRADEMARK OFFICE
OR	Type Customer Number here		
<input checked="" type="checkbox"/> Firm or Individual Name	Lola A. Bartoszewicz		
Address	Sim & McBurney		
Address	330 University Avenue, 6th Floor		
City	Toronto	State	Ontario
Country	Canada	Telephone	416 595 1155
		ZIP	M5G 1R7
		Fax	416 595 1163
ENCLOSED APPLICATION PARTS (check all that apply)			
<input checked="" type="checkbox"/> Specification	Number of Pages	21	<input type="checkbox"/> CD(s), Number
<input type="checkbox"/> Drawing(s)	Number of Sheets		<input checked="" type="checkbox"/> Other (specify)
<input checked="" type="checkbox"/> Application Data Sheet	See 37 CFR 1.76		
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)			
<input checked="" type="checkbox"/>	Applicant claims small entity status. See 37 CFR 1.27.		FILING FEE AMOUNT (\$)
<input type="checkbox"/>	A check or money order is enclosed to cover the filing fees		
<input checked="" type="checkbox"/>	The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number		192253
<input type="checkbox"/>	Payment by credit card. Form PTO-2038 is attached.		\$80.00
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.			
<input checked="" type="checkbox"/>	No		
<input type="checkbox"/>	Yes, the name of the U.S. Government agency and the Government contract number are: _____		

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Lola A. Bartoszewicz

TELEPHONE

416 595 1155

Date

10/08/2002

REGISTRATION NO.

43394

(if appropriate)

Docket Number:

11757-2 LAB

## USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.

P19SMALL/REV05

PTO/SB/17 (11-01)  
Approved for use through 10/31/2002 OMB 0651-0032  
Patent and Trademark Office U.S. DEPARTMENT OF COMMERCE  
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

<b>FEE TRANSMITTAL for FY 2002</b> <i>Patent fees are subject to annual revision</i>		<b>Complete if Known</b>	
		Application Number	
		Filing Date	
		First Named Inventor	Wayne R. Danter
		Examiner Name	
		Group Art Unit	
		Attorney Docket No	11757-2 LAB
<input checked="" type="checkbox"/> Applicant claims small entity status See 37 CFR 1.27			
<b>TOTAL AMOUNT OF PAYMENT</b>		<b>\$80.00</b>	

<b>METHOD OF PAYMENT</b> (check all that apply)		<b>FEE CALCULATION</b> (continued)																																																																																																																									
<input type="checkbox"/> Check <input type="checkbox"/> Credit card <input type="checkbox"/> Money <input type="checkbox"/> Other <input type="checkbox"/> None <input checked="" type="checkbox"/> Deposit Account Deposit Account Number: 192253 Deposit Account Name: Sim & McBurney The Commissioner is authorized to: (check all that apply) <input checked="" type="checkbox"/> Charge fee(s) indicated below <input type="checkbox"/> Credit any overpayments <input type="checkbox"/> Charge any additional fee(s) during the pendency of this application <input type="checkbox"/> Charge fee(s) indicated below, except for the filing fee to the above identified deposit account.		<b>3. ADDITIONAL FEES</b> <table border="1"> <thead> <tr> <th>Large Entity Fee Code (\$)</th> <th>Small Entity Fee Code (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>105</td><td>130</td><td>205 65 Surcharge - late filing fee or oath</td><td></td></tr> <tr><td>127</td><td>50</td><td>227 25 Surcharge - late provisional filing fee or cover sheet</td><td></td></tr> <tr><td>139</td><td>130</td><td>139 130 Non - English specification</td><td></td></tr> <tr><td>147</td><td>2,520</td><td>147 2,520 For filing a request for <i>ex parte</i> reexamination</td><td></td></tr> <tr><td>112</td><td>920*</td><td>112 920* Requesting publication of SIR prior to Examiner action</td><td></td></tr> <tr><td>113</td><td>1,840*</td><td>113 1,840* Requesting publication of SIR after Examiner action</td><td></td></tr> <tr><td>115</td><td>110</td><td>215 55 Extension for reply within first month</td><td></td></tr> <tr><td>116</td><td>400</td><td>216 200 Extension for reply within second month</td><td></td></tr> <tr><td>117</td><td>920</td><td>217 460 Extension for reply within third month</td><td></td></tr> <tr><td>118</td><td>1,440</td><td>218 720 Extension for reply within fourth month</td><td></td></tr> <tr><td>128</td><td>1,980</td><td>228 980 Extension for reply within fifth month</td><td></td></tr> <tr><td>119</td><td>320</td><td>219 160 Notice of Appeal</td><td></td></tr> <tr><td>120</td><td>320</td><td>220 160 Filing a brief in support of an appeal</td><td></td></tr> <tr><td>121</td><td>280</td><td>221 140 Request for oral hearing</td><td></td></tr> <tr><td>138</td><td>1,510</td><td>138 1,510 Petition to institute a public use proceeding</td><td></td></tr> <tr><td>140</td><td>110</td><td>240 55 Petition to revive - unavoidable</td><td></td></tr> <tr><td>141</td><td>1,280</td><td>241 640 Petition to revive - unintentional</td><td></td></tr> <tr><td>142</td><td>1,280</td><td>242 640 Utility issue fee (or reissue)</td><td></td></tr> <tr><td>143</td><td>460</td><td>243 230 Design issue fee</td><td></td></tr> <tr><td>144</td><td>820</td><td>244 310 Plant issue fee</td><td></td></tr> <tr><td>122</td><td>130</td><td>122 130 Petitions to the Commissioner</td><td></td></tr> <tr><td>123</td><td>50</td><td>123 50 Processing fee under 37 CFR § 1.17(q)</td><td></td></tr> <tr><td>126</td><td>180</td><td>126 180 Submission of Information Disclosure Statement</td><td></td></tr> <tr><td>581</td><td>40</td><td>581 40 Recording each patent assignment per property (times number of properties)</td><td></td></tr> <tr><td>148</td><td>740</td><td>246 370 Filing a submission after final rejection (37 CFR § 1.129(a))</td><td></td></tr> <tr><td>149</td><td>740</td><td>249 370 For each additional invention to be examined (37 CFR § 1.129(b))</td><td></td></tr> <tr><td>179</td><td>740</td><td>279 370 Request for Continued Examination (RCE)</td><td></td></tr> <tr><td>169</td><td>900</td><td>169 900 Request for expedited examination of a design application</td><td></td></tr> <tr><td colspan="3">Other fee (specify)</td><td></td></tr> </tbody> </table>		Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid	105	130	205 65 Surcharge - late filing fee or oath		127	50	227 25 Surcharge - late provisional filing fee or cover sheet		139	130	139 130 Non - English specification		147	2,520	147 2,520 For filing a request for <i>ex parte</i> reexamination		112	920*	112 920* Requesting publication of SIR prior to Examiner action		113	1,840*	113 1,840* Requesting publication of SIR after Examiner action		115	110	215 55 Extension for reply within first month		116	400	216 200 Extension for reply within second month		117	920	217 460 Extension for reply within third month		118	1,440	218 720 Extension for reply within fourth month		128	1,980	228 980 Extension for reply within fifth month		119	320	219 160 Notice of Appeal		120	320	220 160 Filing a brief in support of an appeal		121	280	221 140 Request for oral hearing		138	1,510	138 1,510 Petition to institute a public use proceeding		140	110	240 55 Petition to revive - unavoidable		141	1,280	241 640 Petition to revive - unintentional		142	1,280	242 640 Utility issue fee (or reissue)		143	460	243 230 Design issue fee		144	820	244 310 Plant issue fee		122	130	122 130 Petitions to the Commissioner		123	50	123 50 Processing fee under 37 CFR § 1.17(q)		126	180	126 180 Submission of Information Disclosure Statement		581	40	581 40 Recording each patent assignment per property (times number of properties)		148	740	246 370 Filing a submission after final rejection (37 CFR § 1.129(a))		149	740	249 370 For each additional invention to be examined (37 CFR § 1.129(b))		179	740	279 370 Request for Continued Examination (RCE)		169	900	169 900 Request for expedited examination of a design application		Other fee (specify)			
Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid																																																																																																																								
105	130	205 65 Surcharge - late filing fee or oath																																																																																																																									
127	50	227 25 Surcharge - late provisional filing fee or cover sheet																																																																																																																									
139	130	139 130 Non - English specification																																																																																																																									
147	2,520	147 2,520 For filing a request for <i>ex parte</i> reexamination																																																																																																																									
112	920*	112 920* Requesting publication of SIR prior to Examiner action																																																																																																																									
113	1,840*	113 1,840* Requesting publication of SIR after Examiner action																																																																																																																									
115	110	215 55 Extension for reply within first month																																																																																																																									
116	400	216 200 Extension for reply within second month																																																																																																																									
117	920	217 460 Extension for reply within third month																																																																																																																									
118	1,440	218 720 Extension for reply within fourth month																																																																																																																									
128	1,980	228 980 Extension for reply within fifth month																																																																																																																									
119	320	219 160 Notice of Appeal																																																																																																																									
120	320	220 160 Filing a brief in support of an appeal																																																																																																																									
121	280	221 140 Request for oral hearing																																																																																																																									
138	1,510	138 1,510 Petition to institute a public use proceeding																																																																																																																									
140	110	240 55 Petition to revive - unavoidable																																																																																																																									
141	1,280	241 640 Petition to revive - unintentional																																																																																																																									
142	1,280	242 640 Utility issue fee (or reissue)																																																																																																																									
143	460	243 230 Design issue fee																																																																																																																									
144	820	244 310 Plant issue fee																																																																																																																									
122	130	122 130 Petitions to the Commissioner																																																																																																																									
123	50	123 50 Processing fee under 37 CFR § 1.17(q)																																																																																																																									
126	180	126 180 Submission of Information Disclosure Statement																																																																																																																									
581	40	581 40 Recording each patent assignment per property (times number of properties)																																																																																																																									
148	740	246 370 Filing a submission after final rejection (37 CFR § 1.129(a))																																																																																																																									
149	740	249 370 For each additional invention to be examined (37 CFR § 1.129(b))																																																																																																																									
179	740	279 370 Request for Continued Examination (RCE)																																																																																																																									
169	900	169 900 Request for expedited examination of a design application																																																																																																																									
Other fee (specify)																																																																																																																											
<b>1. BASIC FILING FEE</b> <table border="1"> <thead> <tr> <th>Large Entity Fee Code (\$)</th> <th>Small Entity Fee Code (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>101</td><td>740</td><td>201 370 Utility filing fee</td><td></td></tr> <tr><td>106</td><td>330</td><td>206 165 Design filing fee</td><td></td></tr> <tr><td>107</td><td>510</td><td>207 255 Plant filing fee</td><td></td></tr> <tr><td>108</td><td>740</td><td>208 370 Reissue filing fee</td><td></td></tr> <tr><td>114</td><td>160</td><td>214 80 Provisional filing fee</td><td>80.00</td></tr> <tr><td colspan="3"><b>SUBTOTAL (1)</b></td><td><b>\$80.00</b></td></tr> </tbody> </table>		Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid	101	740	201 370 Utility filing fee		106	330	206 165 Design filing fee		107	510	207 255 Plant filing fee		108	740	208 370 Reissue filing fee		114	160	214 80 Provisional filing fee	80.00	<b>SUBTOTAL (1)</b>			<b>\$80.00</b>	<b>2. EXTRA CLAIM FEES FOR UTILITY AND</b> <table border="1"> <thead> <tr> <th>Total Claims</th> <th>Extra Claims</th> <th>Fee from below</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>Independent Claims</td><td>-20** = 0</td><td>X</td><td>0.00</td></tr> <tr><td>Multiple Dependent</td><td>-3** = 0</td><td>X</td><td>0.00</td></tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Large Entity Fee Code (\$)</th> <th>Small Entity Fee Code (\$)</th> <th>Fee Description</th> <th>Fee Paid</th> </tr> </thead> <tbody> <tr><td>103</td><td>18</td><td>203 9 Claims in excess of 20</td><td></td></tr> <tr><td>102</td><td>84</td><td>202 42 Independent claims in excess of 3</td><td></td></tr> <tr><td>104</td><td>280</td><td>204 140 Multiple dependent claim, if not paid</td><td></td></tr> <tr><td>109</td><td>84</td><td>209 42 ** Reissue independent claims over original patent</td><td></td></tr> <tr><td>110</td><td>18</td><td>210 9 ** Reissue claims in excess of 20 and over original patent</td><td></td></tr> <tr><td colspan="3"><b>SUBTOTAL (2)</b></td><td><b>\$0.00</b></td></tr> </tbody> </table>		Total Claims	Extra Claims	Fee from below	Fee Paid	Independent Claims	-20** = 0	X	0.00	Multiple Dependent	-3** = 0	X	0.00	Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid	103	18	203 9 Claims in excess of 20		102	84	202 42 Independent claims in excess of 3		104	280	204 140 Multiple dependent claim, if not paid		109	84	209 42 ** Reissue independent claims over original patent		110	18	210 9 ** Reissue claims in excess of 20 and over original patent		<b>SUBTOTAL (2)</b>			<b>\$0.00</b>																																																				
Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid																																																																																																																								
101	740	201 370 Utility filing fee																																																																																																																									
106	330	206 165 Design filing fee																																																																																																																									
107	510	207 255 Plant filing fee																																																																																																																									
108	740	208 370 Reissue filing fee																																																																																																																									
114	160	214 80 Provisional filing fee	80.00																																																																																																																								
<b>SUBTOTAL (1)</b>			<b>\$80.00</b>																																																																																																																								
Total Claims	Extra Claims	Fee from below	Fee Paid																																																																																																																								
Independent Claims	-20** = 0	X	0.00																																																																																																																								
Multiple Dependent	-3** = 0	X	0.00																																																																																																																								
Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid																																																																																																																								
103	18	203 9 Claims in excess of 20																																																																																																																									
102	84	202 42 Independent claims in excess of 3																																																																																																																									
104	280	204 140 Multiple dependent claim, if not paid																																																																																																																									
109	84	209 42 ** Reissue independent claims over original patent																																																																																																																									
110	18	210 9 ** Reissue claims in excess of 20 and over original patent																																																																																																																									
<b>SUBTOTAL (2)</b>			<b>\$0.00</b>																																																																																																																								
**or number previously paid, if greater; For Reissues, see above		*Reduced by Basic Filing Fee Paid <b>SUBTOTAL (3)</b>																																																																																																																									

<b>SUBMITTED BY</b>		<b>Complete (if applicable)</b>	
Name (Print/Type)	Lois A. Szytoszewicz	Registration No (Attorney/Agent)	41394
Signature		Telephone	416 595 1155 ext 200
		Date	October 8, 2002

**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on

**Burden Hour Statement:** This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

**TRANSMITTAL LETTER**  
**(General - Patent Pending)**

Docket No.  
**11757-2 LAB**

In Re Application Of:

**Wayne R. Danter**

Serial No.

Filing Date

Examiner

Group Art Unit

Title:

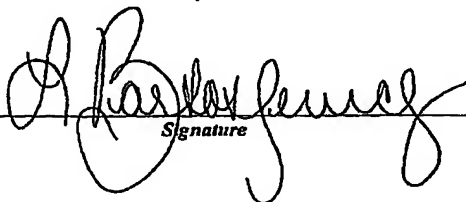
**PROTEIN TYROSINE KINASE INHIBITORS****TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:**

Transmitted herewith is:

**Provisional Application for Patent Cover Sheet**  
**Application Data Sheet**  
**Fee Transmittal for FY 2002**  
**Specification - 21 pages**

In the above identified application.

- ☐ No additional fee is required.
- ☐ A check in the amount of \_\_\_\_\_ is attached.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **192253** as described below. A duplicate copy of this sheet is enclosed.
- ☒ Charge the amount of **\$80.00**
- ☐ Credit any overpayment.
- ☐ Charge any additional fee required.


  
 Signature
Dated: **October 8, 2002**

I certify that this document and fee is being deposited  
 on **October 8, 2002** with the U.S. Postal Service as  
 first class mail under 37 C.F.R. 1.8 and is addressed to the  
 Commissioner of Patents and Trademarks, Washington,  
 D.C. 20231.


  
 Signature of Person Mailing Correspondence
**Cheryl Alphonso**

Typed or Printed Name of Person Mailing Correspondence

CC:

**Initial Information Data Sheet****Inventor Information**

Inventor One Given Name:: Wayne R.  
Family Name: Danter  
Postal Address Line One:: 147 Chesham Ave.,  
City:: London  
State or Province:: Ontario  
Postal or Zip Code:: N6G 3V2  
Citizenship Country:: Canada

**Correspondence Information**

Name Line One:: Lola A. Bartoszewicz  
Name Line Two:: Sim & McBurney  
Address Line One: 330 University Avenue  
Address Line Two: 6<sup>th</sup> Floor  
City:: Toronto  
State or Province:: Ontario  
Postal or Zip Code:: M5G 1R7  
Telephone One:: 416 595 1155  
Fax:: 416 595 1163  
Electronic Mail:: [bartoszewicz@sim-mcburney.com](mailto:bartoszewicz@sim-mcburney.com)

**Application Information**

Title Line One:: Protein Tyrosine Kinase Inhibitors  
Total Drawing Sheets::  
Formal Drawings::  
Application Type:: Utility  
Docket Number:: 11757-2 LAB

Representative Customer Number:: 24223  
Registration Number:: 43394

## Protein Tyrosine Kinase Inhibitors

### Field of the Invention

The present invention relates to compounds which inhibit, regulate  
5 and/or modulate tyrosine kinase signal transduction and methods of using  
such compounds to treat tyrosine kinase-dependent diseases and  
conditions in mammals.

### Background of the Invention

10 Throughout this application, various references are cited in  
parentheses to describe more fully the state of the art to which this invention  
pertains. The disclosure of these references are hereby incorporated by  
reference into the present disclosure.

Tyrosine kinases are a class of enzymes that catalyze the transfer  
15 of the terminal phosphate of adenosine triphosphate to tyrosine residues  
in protein substrates. Tyrosine kinases are believed, by way of substrate  
phosphorylation, to play critical roles in signal transduction for a number  
of cell functions. Though the exact mechanisms of signal transduction is  
still unclear, tyrosine kinases have been shown to be important  
20 contributing factors in cell proliferation, carcinogenesis and cell  
differentiation.

Tyrosine kinases can be categorized as receptor type or non-  
receptor type. Receptor type tyrosine kinases have an extracellular, a  
transmembrane, and an intracellular portion, while non-receptor type  
25 tyrosine kinases are wholly intracellular.

The receptor-type tyrosine kinases are comprised of a large  
number of transmembrane receptors with diverse biological activity.  
Approximately, 20 different subfamilies of receptor-type tyrosine kinases  
have been identified. One tyrosine kinase subfamily is comprised of  
30 EGFR, HER2, HER3, and HER4. Ligands of this subfamily of receptors  
include epithelial growth factor, TGF- $\alpha$ , amphiregulin, HB-EGF,

betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF- $\alpha$  and  $\beta$  receptors, CSFIR, c-kit and FLK-II. The FLK family is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1) (Plowman et al., DN&P 7(6):334-339, 1994, which is hereby incorporated by reference).

The non-receptor type of tyrosine kinases are also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis (Bolen Oncogene, 8:2025-2031 (1993), which is hereby incorporated by reference).

Both receptor-type and non-receptor type tyrosine kinases are implicated in cellular signalling pathways leading to numerous pathogenic conditions, including a variety of cancers. For example, the Bcr-Abl tyrosine kinase is the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). Inappropriate Bcr-Abl activity is also demonstrated in murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Drug screening has been used *in vitro* to try and identify new compounds with potential cell line-specific anti-tumour activity. Such a screening was published with respect to the compound 2,5-pyridinedicarboxamide, N,N'-bis[4-(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)phenyl]-, dihydrochloride (also known as 2,5-pyridinedicarboxanilide, 4',4''-bis(1,4,5,6-tetrahydro-5-methyl-2-pyrimidinyl)-, dihydrochloride trihydrate) (National Cancer Institute 1965)

which was not identified as a protein tyrosine kinase inhibitor. The screening conducted using a leukemia mouse model was not conclusive.

It has now been identified that the aforementioned compound herein referred to as "COTI-001" is involved in the signal transduction of tyrosine kinases and in particular those tyrosine kinases involved in various malignancies leading to the use of such compound in methods to effectively treat a variety of cancers in mammals.

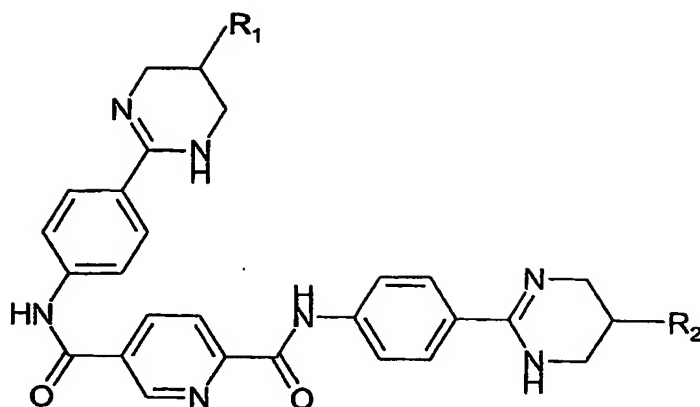
#### Summary of the Invention

10 The present invention relates to the identification of the role of COTI-001 to inhibit, regulate and/or modulate tyrosine kinase signal transduction to treat tyrosine kinase-dependent diseases and conditions, such as cancer and tumour growth, and the like in mammals.

15 More particularly, the present invention relates to COTI-001 compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds are novel protein tyrosine kinase inhibitors useful in the treatment of a variety of malignancies involving inappropriate tyrosine kinase activity.

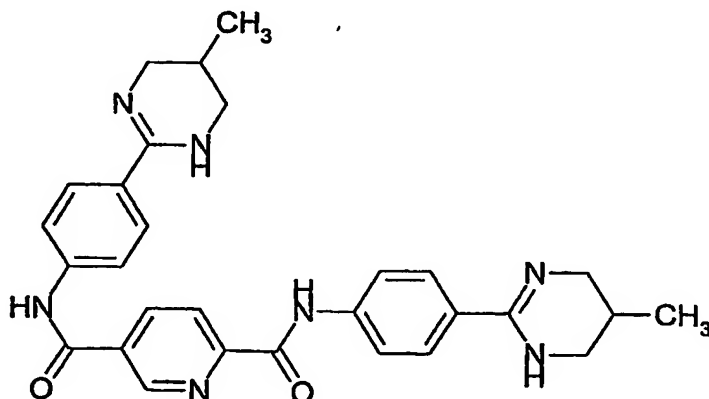
20 One embodiment of the present invention is illustrated by a compound of Formula I, and the pharmaceutically acceptable salts and stereoisomers thereof:





wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with halogen, an alkyl, alkenyl, and alkynyl;  $NZ_1Z_2$ , wherein  $Z_1$  and  $Z_2$  are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.

In one aspect of the present invention, the compound is represented as formula II:



and the pharmaceutically acceptable salts and stereoisomers thereof.

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula I together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a pharmaceutical composition which is comprised of a compound in accordance with formula II together with a pharmaceutically acceptable carrier.

According to another aspect of the present invention is a method of treating or preventing cancer involving inappropriate tyrosine kinase activity in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of formula I or II.

According to another aspect of the present invention is a method of treating cancer or preventing cancer using a composition comprising a compound of formula I or II wherein the cancer is selected from cancers of the breast, leukemias, melanoma, stomach, colon, CNS, ovarian and prostate and those listed in Table I.

According to still another aspect of the present invention is a method of treating or preventing cancer comprising administration of a therapeutically effective amount of a composition comprising a compound of formula I or II wherein the cancer is chronic myeloid leukemia (CML).

According to another aspect of the present invention is a method of treating or preventing a tyrosine kinase-dependent disease or condition which comprises administering a therapeutically effective amount of a compound selected from the group consisting of formula I and formula II.

According to another aspect of the present invention is the use of a compound of formula I and/or II in a medicament for the treatment of a disease condition involving inappropriate tyrosine kinase activity.

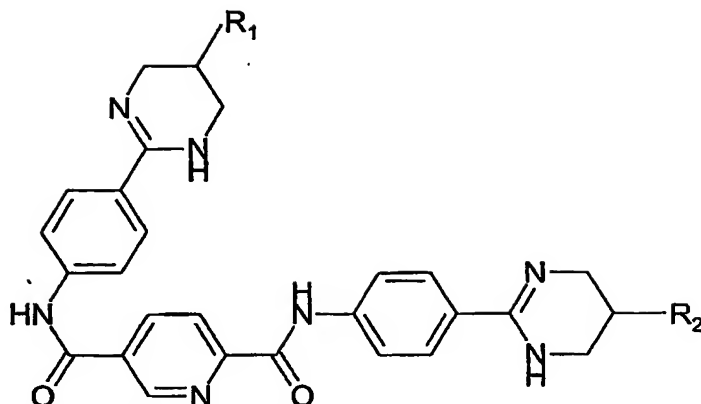
According to still a further aspect of the present invention is a method for the treatment of a tyrosine-kinase dependent disease or condition comprising administering a therapeutically effective amount of a composition comprising a compound of formula I further comprising a  
5 second compound selected from the group consisting of an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent, an anti-proliferative agent, a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth  
10 factor, an MMP inhibitor, an integrin blocker, interferon- $\alpha$ , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, and troponin-1, tamoxifen and raloxifene.

According to a further aspect of the present invention is a method of  
15 treating cancer which comprises administering a therapeutically effective amount of a compound of formula I or II or pharmaceutically acceptable salts thereof in combination with a therapy selected from the group consisting of radiation therapy and chemotherapy.

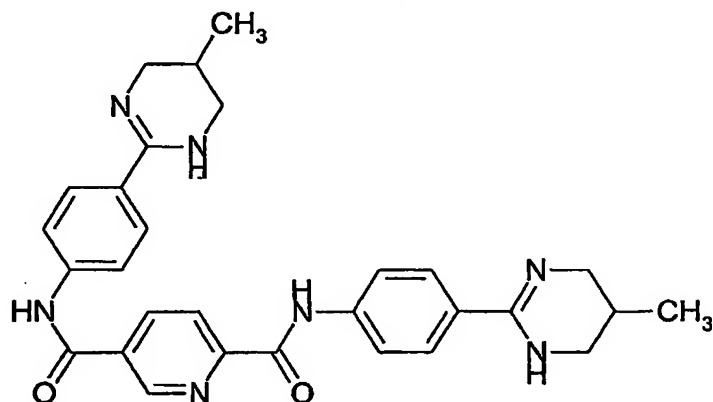
Other features and advantages of the present invention will become  
20 apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from said  
25 detailed description.

#### Detailed Description of the Preferred Embodiments

The compound of this invention is illustrated by Formula I or a pharmaceutically acceptable salt or stereoisomer thereof:



wherein  $R_1$  and  $R_2$  are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with  
 5 halogen, an alkyl, alkenyl, and alkynyl;  $NZ_1Z_2$ , wherein  $Z_1$  and  $Z_2$  are



independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.

10 Yet another embodiment of the present invention is a compound which is selected from the group consisting of

as well as pharmaceutically acceptable salts or stereoisomers thereof.

Using an *in silico* assay, the COTI-001 compound of the present invention has been demonstrated and predicted to have *in vitro* activity against a variety of cancerous cell types shown in Table 1. Also, while not explicitly shown, the COTI-001 compound of Formula I has predicted  
5 *in vitro* activity against HIV.

Included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or  
10 preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Preferred cancers for treatment are selected from cancers of the breast, colon, prostate, gastric, melanoma, ovarian and leukemias. Another preferred form of cancer is chronic  
15 myeloid leukemia (CML).

The invention also encompasses pharmaceutical compositions comprising a compound of Formula I or II as well as pharmaceutically acceptable salts thereof for the treatment of HIV.

The compositions and methods of the invention can include a  
20 compound of Formula I or II.

Also included is a method of treating or preventing a tyrosine kinase-dependent disease or condition in a mammal which comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Formula I or II. The  
25 therapeutic amount varies according to the specific disease and is discernible to the skilled artisan without undue experimentation.

Also included in the scope of the claims is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I or Formula II in combination with radiation  
30 therapy and/or in combination with a compound generally known to for use in selected cancers and selected from the group consisting of an

estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic agent and an antiproliferative agent. These and other aspects of the invention will be apparent from the teachings contained herein.

5 "Tyrosine kinase-dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more tyrosine kinases. Tyrosine kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion and migration, and differentiation. Diseases  
10 associated with tyrosine kinase activities include but are not limited to the proliferation of tumor cells.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E. L. Eliel and S. H. Wilen, Stereo-chemistry of Carbon Compounds, John Wiley & Sons,  
15 New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by  
20 the scope of the invention, even though only one tautomeric structure is depicted.

As used herein, "alkyl" is intended to include both branched, straight-chain, and cyclic saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C<sub>1</sub>-C<sub>10</sub>, as in "C<sub>1</sub>-  
25 alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear, branched, or cyclic arrangement. For example, "C<sub>1</sub>-C<sub>10</sub> alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on, as well as cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydro-naphthalene,  
30 methylenecyclohexyl, and so on. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C<sub>2</sub>-C<sub>6</sub> alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C<sub>2</sub>-C<sub>6</sub> alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazoyl, cinnolinyl, quinoxalinyl, pyrrazoyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl,

indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo. The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranal, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranal, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof.



The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from

5 inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic,

10 methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods.

15 Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the

20 appropriate inorganic or organic base.

The compounds of this invention may be prepared by employing reactions and standard manipulations that are known in the literature or exemplified in the experimental procedures.

The instant compounds are useful as pharmaceutical agents for

25 mammals, especially for humans, in the treatment of tyrosine kinase dependent diseases and in particular the treatment of various cancers.

The compounds of the instant invention may be administered to patients for use in the treatment of cancer.

The compounds of this invention may be administered to

30 mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with

known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The compounds of the instant invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadministered with radiation therapy. The synergistic effects of

inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186). "Estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyloxy)ph- enyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

10 "Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5.alpha.-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

15 "Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, alpha-difluoromethylomithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide and N-4-carboxyphenyl retinamide.

20 "Cytotoxic agents" refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin,

irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(c-hloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-  
 5 (11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino- -13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridiny-4-methylsulphonyl-  
 10 daunor- ubicin (see WO 00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-  
 15 N-(- 3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L'-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS 188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-  
 20 kl]acridine- -2-(6H)propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methy- -1H,12H benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H) dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide,  
 25 sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazo- le-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)-ethyl]-N-methylamino]ethyl]-5-[4-Hydroxy-3,5-dimethoxyphenyl]-  
 30 5,5a,6,8,8a,- 9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-

phenanthridiniu- m, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-- 9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2-,1-c]quinolin-7-one, and dimesna.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxy- cytidine, N-[5-(2,3'-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl) urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycer- o-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b] [1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes, such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example).

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-

dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH1382, genistein, ST1571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo [2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, ST1571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalaz- inamine, and EMD121974.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the

biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to  
5 administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

The present invention also encompasses a pharmaceutical  
10 composition useful in the treatment of cancer, particularly cancers involving inappropriate tyrosine kinase activity, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions  
15 comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered into  
a human subject, the daily dosage will normally be determined by the  
20 prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer.  
25 Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The above disclosure generally describes the present invention. A  
30 more complete understanding can be obtained by reference to the following specific Examples. These Examples are described solely for purposes of

illustration and are not intended to limit the scope of the invention. Changes in form and substitution of equivalents are contemplated as circumstances may suggest or render expedient. Although specific terms have been employed herein, such terms are intended in a descriptive sense and not for purposes of limitation.

### Examples

The examples are described for the purposes of illustration and are not intended to limit the scope of the invention.

Methods of synthetic chemistry, protein and peptide biochemistry, molecular biology, and pharmacology referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art.

#### Example 1

Molecules with the potential target biological activity were analyzed in a validated *in silico* assay that is based on public domain National Cancer Institute *in vitro* anti-cancer data. The molecules are first decomposed to 110 descriptors using a proprietary CHEMSAS™ algorithm. This decomposition process results in a molecular data pattern of 110 variables that is then input into the *in silico* model. The output of the model is a prediction of the -Log(GI50) for the molecule(s) being analyzed against the specific cancer cell type in question i.e., breast cancer or leukemia, etc. A specific *in silico* assay was also developed for the leukemia cell line (i.e. K562) that over expresses the abnormal protein tyrosine kinase found in Chronic Myelogenous Leukemia (CML). Results of the *in silico* assay for molecular Formulas I and II in a number of cancer cell types are summarized below in Table 1.

#### Table One



20

Compound	leukemia	K562(CML)*	NSCLC**	SCLC***	Colon	CNS
Formula I/II	-5.39	-5.64	-4.89	-4.78	-5.16	-4.92

Compound	Melanoma	Ovary	Renal	Prostate	Breast
5 Formula I/II	-4.72	-4.84	-4.82	-5.13	-4.60

Note: Values in the table refer to the  $-\text{Log}(\text{G150})$  as a molar concentration.

10 If  $-\text{Log}(\text{G150}) > -4.5$  then the compound is likely to be inactive.

If  $-\text{Log}(\text{G150}) > -5$  and  $< -4.5$  then the compound is likely to have some *in vitro* activity.

If  $-\text{Log}(\text{G150}) < -5$  then the compound is considered to have *in vitro* activity.

15 \*K562 is a specific leukemia cell line for CML that over expresses the abnormal protein tyrosine kinase.

\*\* NSCLC is a non small cell lung cancer

\*\*\*SCLC is a small cell lung cancer

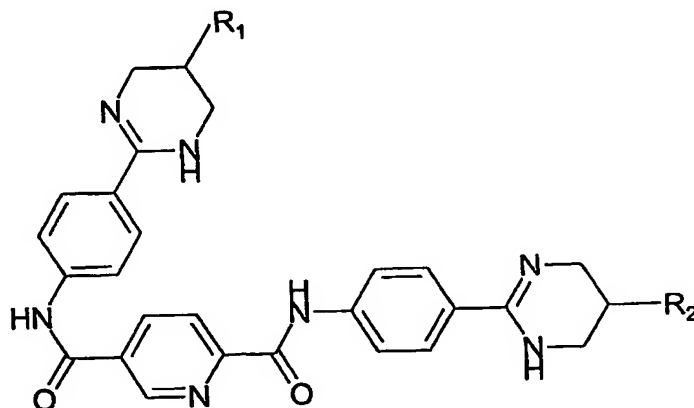
20

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention.

25

**Abstract**

The present invention relates to uses of the compounds of Formula I as well as pharmaceutically acceptable salts and stereoisomers thereof in methods to treat a variety of tumors in mammals involving abnormal  
5 tyrosine kinase signalling, the compounds represented as:



wherein R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of H; alkyl; alkenyl; alkynyl; halogen; aryl; heteroaryl containing N, O, or S; the aryl and heteroaryl may be further substituted with  
10 halogen, an alkyl, alkenyl, and alkynyl; NZ<sub>1</sub>Z<sub>2</sub>, wherein Z<sub>1</sub> and Z<sub>2</sub> are independently selected from the group consisting of H and alkyl; and (CO)Y wherein Y is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, heteroaryl containing N, O, or S, and the aryl and heteroaryl may be further substituted with halogen, alkyl, alkenyl, and alkynyl.

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☒ BLACK BORDERS

☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES

☐ FADED TEXT OR DRAWING

☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING

☐ SKEWED/SLANTED IMAGES

☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS

☐ GRAY SCALE DOCUMENTS

☒ LINES OR MARKS ON ORIGINAL DOCUMENT

☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**